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Monacolin K as a Natural Alternative for Synthetic Statins

Kozakiewicz Julia
University Clinical Hospital in Bialystok
ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland
kozakiewiczjulia99@gmail.com
ORCID: 0009-0002-5435-3007

Okońska Aleksandra
University Clinical Hospital in Bialystok
ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland
aokonska.stn@gmail.com
ORCID: 0009-0001-9036-7150

Ziemba Michał
University Clinical Hospital in Bialystok
ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland
michal.ziemba98@gmail.com
ORCID: 0009-0003-2200-431X

Kościelecki Kamil
University Clinical Hospital in Bialystok
ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland
kamilkoscielecki99@gmail.com
ORCID: 0009-0001-5516-7540

Kalisz Agnieszka
University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a
15-276 Białystok, Poland
kalisz.a39@gmail.com
ORCID: 0009-0001-2996-7691

Krakowiak Magdalena
University Clinical Hospital in Bialystok
ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland
krakmagdalena@gmail.com
ORCID: 0009-0002-8600-2199

Kaczmarek Aleksandra
University Clinical Hospital in Bialystok
ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland
aleksandra.kośmider.29@gmail.com
ORCID: 0009-0006-3494-7990

ABSTRACT

Introduction: This review paper aims to verify the safety of monacolin K, examine the effect on blood cholesterol levels, discuss the contribution to the reduction of cardiovascular risk and indicate examples of pleiotropic effects of this substance.

Materials and methods: A review of chosen literature in the PubMed database was conducted, using the following key words: „Monacolin K", „Hypercholesterolemia", „Red yeast rice", „Supplementation".

Summary: Monacolin K is considered to be natural statin contained in fermented red rice or oyster mushroom. The use of monacolin K may contribute to the development of mild muscle pain or rhabdomyolysis, but it is noticed less frequently than in treatment with synthetic statins. In addition, there are also concerns about liver and/or kidney damage, headaches and/or dizziness, musculoskeletal symptoms and gastrointestinal disturbances in some people, especially when high doses of monacolin K are used. Monacolin K lowers the level of cholesterol in the blood and contributes to reducing the risk of cardiovascular diseases. Furthermore, monacolin K has anti-inflammatory effects and anti-cancer mechanisms.

Conclusions: Monacolin K improves the lipid profile by lowering low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total cholesterol (TC) levels which indirectly reduces the cardiovascular risk with less frequently observed side effects. Monacolin K has many pleiotropic effects like anti-inflammatory and anti-cancer mechanisms by inhibiting cancer cell proliferation and stimulating apoptosis. It should be emphasized that the long-term safety of regular use of these preparations has not been fully documented. Some people taking these supplements experience side effects similar to those seen with statins. Both health benefits and side effects should be further investigated in future studies.
Keywords: monacolin K, hypercholesterolemia, red yeast rice, supplementation

Introduction

These days more and more people choose alternative medicine instead of medicine confirmed by many years of clinical research. It consists of a wide range of practices, products and therapies - from those that are biologically plausible, but not well tested to those with known harmful and toxic effects. It is crucial to investigate the harmful and positive effects of these therapies in future studies because the demand for them continues to grow.
The example of alternative drug is monakolin K-natural statin.

Statins are a class of medications that are commonly used to lower cholesterol levels in the blood. They work by inhibiting an enzyme in the liver that plays a key role in the production of cholesterol [1]. Statins are prescribed to reduce the risk of heart disease and stroke in individuals with high cholesterol levels [2]. Synthetic statins are generally well tolerated, a minority of patients suffer from side effects like muscle pain or weakness, headache, gastrointestinal symptoms [3]. But, what about natural statins?

Monacolin K is a naturally occurring compound found in fermented red rice or oyster mushroom. It is chemically identical to the active ingredient in the prescription medication-lovastatin so the effect of the drug is the same. It is believed that 'natural' agents do not have side effects but structural similarity with synthetic statin implies that adverse reactions can also be expected.

Safety of monacolin K

Monacolin K is considered to be safe for humans and may be an alternative for patients who cannot tolerate statins in the treatment of dyslipidemia and reducing cardiovascular risk.

Treatment by monacolin K may be associated with side effects like allergy or hypersensitivity which are observed during taking any other drugs. Clinical studies have shown that monacolin K supplementation was not associated with an increased incidence of musculoskeletal disorders like myopathy or rhabdomyolysis, compared to the group not using this therapy. Additionally, a reduced risk of rash, dizziness, constipation, joint pain and liver dysfunction has been demonstrated [4]. It has been proven that the incidence of liver dysfunction and kidney damage was the same in the group taking red yeast rice extract as in the control group- not taking statins. The reported incidence of muscle symptoms was lower in the red yeast rice extract treated population compared with control groups- not using statins. Rhabdomyolysis or myopathy with increased CK levels > 10 times the upper limit of normal were not observed in any of the studies [5]. In a study with eighteen people who were randomly allocated to receive 2 mg monacolin K or diet therapy alone for 8 weeks we can conclude that patients in the monacolin K group exhibited significant reductions in cholesterol, blood pressure without any recognised adverse effect [6].

Another clinical case study proved that natural statins are not free from side effects typical for this group of drugs. A rhabdomyolysis manifests itself as chest discomfort and generalized myalgia was observed during eating red yeast rice by a 50-years old woman in order to reduce her cholesterol levels [7]. During analyzing this case we should take into consideration accompanying medical conditions, drugs interactions and different substances contained in red rice. The safety profile of monacolin K is based mostly on case reports, and the assessment is complicated by self-medication and variable product composition, polypharmacy, comorbidities and doses. To determine the usefulness of monacolin K in clinical practice, monitoring for side effects should become a priority in future studies, which must include patients at risk of statin intolerance.

For now, we should remember that monacolin K is contained in dietary supplements which are not as adequately tested or regulated as medical drugs. We should take into account potential side effects. Only if the mild side effect profile of these preparations is confirmed, can they constitute a safe and effective option for treating dyslipidemia and reducing cardiovascular risk.

Cardiovascular risk and hyperlipidemia

Despite revolutionary improvements in global health conditions over recent decades, the leading cause of death and disability is cardiovascular disease (CVD). One of the main risk factor of CVD is hypercholesterolemia [8].The cornerstone of treatment of hypercholesterolemia is a healthy lifestyle, including diet and physical activity, an optimum weight, no smoking and appropriate pharmacotherapy.

The mainstay of pharmacological treatment are statins which can reduce LDL-C concentration by an average of 1.8 mmol/l. Consequently reducing the risk of Ischemic Heart Disease by approximately 60% and stroke by 17% [9].

Monacolin K as a natural statin imitates the action of the synthetic statins. In a double-blind, randomized, placebo-controlled trial, 52 physicians and their spouses with elevated total cholesterol levels were randomly assigned to receive monacolin K or placebo for 8 weeks. It has been proven that in the monacolin K group LDL-cholesterol level was reduced by 22% and total cholesterol by 15%. This result was statistically significant compared to the group

without supplementation [10]. It has been proven that 3-month-long supplementation monacolin K with vitamin C, vitamin K2 and vitamin B1 leads to reduction in total cholesterol (TC), LDL-cholesterol (LDL-C), and triglycerides (TG) concentrations [11]. Not only the duration of monacolin k supplementation is important but also the dose.

A meta analysis conducted in 2014, including 804 participants with hypercholesterolemia in 13 randomized controlled trials, proved that supplementation with red yeast rice (at a dose of monacolin K from 2 to 11.4 mg) significantly lowered serum concentrations of total cholesterol (TC), triglycerides (TG) and LDL-cholesterol (LDL-C) in compared to placebo. No serious side effects have been reported [12].

In another study, a 15% LDL-cholesterol (LDL-C) reduction was noticed in response to a supplementation of 3 mg monacolin K within 12 weeks [13]. Eighty-three healthy people with hyperlipidemia were enrolled in the clinical study and divided into a group with monacolin K supplementation (2.4 g/day) or placebo. The results showed that after 8 weeks of therapy, total cholesterol (TC), LDL-cholesterol (LDL-C), and triglycerides (TG) levels decreased, while HDL-cholesterol (HDL-C) did not change significantly [14].

With similarities in chemical, pharmacokinetic and pharmacodynamic properties between lovastatin and monacolin K, we expect the effects of red yeast rice and lovastatin to be similar. In systematic review, we can point out differences in effect between red yeast rice and simvastatin. The daily dose of red yeast rice used in the trials ranged from 1.2 to 3.6 g, whereas simvastatin daily dose was 10 mg or 20 mg. Red yeast rice and simvastatin did not show any statistically significant difference in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides levels (TG) [15].

The effect of monacolin K can be enhanced by other natural substances like berberine, polyphenolic extract of annurca apple. This nutraceutical combination in 6 months therapy reduces by 19.2% in total cholesterol (TC), 19.8% in low-density lipoprotein (LDL-C) and 23% triglycerides (TG) levels [16].

Similar results, i.e demonstrating a beneficial effect on lipid metabolism, are confirmed by a study in which monacolin K was supplemented with astaxanthin in association with a low-energy/fat diet [17].

Based on double-blind, placebo-controlled randomized clinical trial, it appears that a nutraceutical containing 10 mg of monacolin K along with antioxidants safely reduces cholesterolemia, hs-CRP and improves endothelial function [18].

In a randomized trial in people who supplement 10.82 mg of monacolin K and 9.32 mg of hydroxytyrosol-olive fruit extract results show a 24% decrease of low-density lipoprotein (LDL-C) concentrations, smaller but significant decrease of total cholesterol (TC), apoB, and triglycerides (TG).

Both systolic and diastolic blood pressure decreased by 10 and 7 mmHg respectively [19].

Another study proved that monacolin K has a beneficial effect on blood cholesterol levels by decreasing in low-density lipoproteins (LDL-C), total cholesterol (TC), apolipoprotein concentration and also blood pressure [6].

It is suggested that red yeast rice is an effective and relatively safe method of treating dyslipidemia which is associated with lower cardiovascular risk. However, further research is still warranted before red yeast rice can be recommended to patients with dyslipidemia, especially as an alternative to statins.

Pleiotropic effects

In this review we mostly focused on the main effect of monacolin K, which is reducing blood cholesterol levels by inhibiting the enzyme responsible for cholesterol production in the liver. In addition, macolin K has anti-inflammatory, antioxidant, antibacterial and anticancer properties.

Statins have some links with the development of cancer. There are researchers suggesting that statins may have potential anti-cancer effects by inhibiting the proliferation of cancer cells, inducing apoptosis (programmed cell death) and reducing inflammatory processes that may contribute to the development of cancer. The anti-angiogenic activities also may be significant for cancer therapy.

It has been shown that ovarian, endometrial and cervical cancer cells undergo apoptosis in the presence of lipophilic statins - lovastatin and simvastatin depending on the dose and time, no such effect was observed for the hydrophilic statin - pravastatin.

Synergistic effects was demonstrated on cell viability by combining statins and chemotherapy in primary ovarian and uterine cancer tissue cultures [20]. Another study confirms that simvastatin inhibits the growth of cancer cells more effectively than the hydrophilic pravastatin [21].

A retrospective cohort study confirms that statins were associated with a decreased risk in mortality with pancreatic cancer patients, especially with simvastatin and atorvastatin users. The level of cholesterol was not associated with mortality [22].

Data from prospective observational studies confirm a lower risk of advanced prostate cancer and reduced mortality in people using statins compared to people not using statins [23].

There is a scientifically proven relationship between overweight, obesity and consequently, metabolic disorders such as hypercholesterolemia, which may have a negative impact on the prognosis of breast cancer patients. Future studies should clearly evaluate the relationship between host factors (e.g., obesity/hypercholesterolemia), drug therapy (e.g., statins), and breast cancer progression [24].

Epidemiological studies show a relationship between the use of statins and a reduced risk of colorectal cancer. In a study on human colon cancer cell lines chinese red yeast rice containing monacolin both inhibited the growth of cancer cells and increased their apoptosis [25]. Analyzes of 1,953 patients with colorectal cancer and a control group from 2015 showed that the use of statins for at least five years was associated with a reduction of relative risk of colorectal cancer after taking into account other known risk factors, e.g. use or absence of aspirin or other non-steroidal anti-inflammatory drugs; presence or absence of physical activity, hypercholesterolemia, family history of colon cancer [26].

It should be noted that there is currently no clear evidence on the exact effect of statins on cancer development. Further research is necessary to better understand the associations between statins and cancer risk and to determine whether there are any benefits or risks associated with their use in the context of cancer.

In a study conducted on 24 people after 26 weeks of treatment with monacolin K, a mild decrease in the HOMA index was found, which indicated an improvement in insulin sensitivity. Plasma triglycerides (TG), total cholesterol (TC) and LDL-cholesterol(LDL-C) levels and ALT activity in liver function tests were significantly reduced. Indirectly, the changes can be associated with a reduction in oxidative stress.

Important limitations of the study should be taken into account: the lack of a placebo control group and the small number of patients [27].

In a randomized clinical trial involving 25 people, it was proven that 10 mg of monacolin appears to reduce high-sensitivity C-reactive protein (hs-CRP) through an indirect anti-inflammatory effect and reducing markers of vascular remodeling which appears to be associated with marked improvement in cardiovascular risk [18].

Published in 2021 study provides evidence for the possible anti-inflammatory effects of red rice extract through a pathway mediated by STING in immune cells. Several studies have described that STING has a regulatory function in autoimmune, cancer and inflammatory diseases [28][29]. Moreover, the production of inflammatory cytokines IFN-γ and NO was decreased whereas the immunosuppressive cytokine IL-10 increased [30].

Summary and conclusions

This article outlines the beneficial effects of monacolin K, possible side effects, potential pleiotropic effects and indicates how much research must be carried out in the future to determine the correct principles of pharmacotherapy using monacolin K.

Monacolin K is an active substance contained in red rice yeast, which has the ability to lower blood cholesterol levels by inhibiting the enzyme responsible for cholesterol production in the liver. Monacolin K works by reducing the synthesis of endogenous cholesterol and increasing the liver's ability to remove cholesterol from the blood. Thanks to this, monacolin K can help regulate cholesterol levels, which may help reduce the risk of cardiovascular diseases such as atherosclerosis, stroke or heart attack. However, it is necessary to remember that monacolin K may cause side effects like: allergies, myopathy, rhabdomyolysis, gastrointestinal symptoms and interactions with other drugs, so it is always worth consulting a doctor before starting supplementation.

Many studies try to prove its beneficial effects and including in anti-inflammatory therapy. Monacolin K will also remain of interest to scientists due to its potential anti-cancer effects.

Further studies should be considered to confirm the safety and effects of monacolin K.

Disclosure

Author's contribution

Conceptualization: Julia Kozakiewicz

Methodology: Julia Kozakiewicz, Aleksandra Okońska,

Formal analysis: Kamil Kościelecki, Aleksandra Kaczmarek, Magdalena Krakowiak

Investigation: Magdalena Krakowiak, Agnieszka Kalisz

Writing-rough preparation: Julia Kozakiewicz, Aleksandra Kaczmarek, Agnieszka Kalisz

Writing-review and editing: Kamil Kościelecki, Agnieszka Kalisz, Aleksandra Okońska,

Supervision: Michał Ziemba

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